II. REMARKS

Claims 1-32 have been presented in this application. All subject matter, except that of original claims 1-11 has been determined by the Examiner to be drawn to non-elected subject matter. Applicants have previously cancelled claims 1-22. Claims 23-32, were not entered by the Examiner and are cancelled by the present communication without prejudice. To more particularly define the subject matter of the elected invention, Applicants have added new claims 33-43, which incorporate the subject matter of original claims 1-11. The new claims add no new matter, being fully supported by the Specification and original claims 1-11 of this application. Upon entry of the present amendment, claims 33-43 will be pending in this application.

C. The Rejection Under 35 U.S.C. § 112

The objection to the specification and corresponding rejection of claims 1-7 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement are respectfully traversed. Claims 1-7 have been cancelled, thereby rendering the rejection moot. However, in order to be fully responsive to the Office Action, Applicants will address the rejection as to new claims 33-43.

It is acknowledged in the Office Action that the specification is enabling for extending the life span of a Drosophila by administering the histone deacetylase inhibitor 4-phenylbutyric acid. It is alleged, however, that the specification provides no guidance for subjects other than Drosophila or histone deacetylase inhibitors other than 4-phenylbutyric acid. As such, it is alleged that undue experimentation would have been required for one skilled in the art to practice the claimed methods.

However, Applicants submit that Drosophila is currently accepted by the scientific community as a model system that is predictive of outcomes in other organisms. For example, the specification discloses that the Drosophila is an accepted model organism for the study of disease in other organisms (see, for example, page 13, line 26, to page 14, line 16). The specification further discloses that the effects of the histone deacetylase inhibitor 4-phenylbutyric acid in Drosophila, as described in the current specification, are consistent with molecular effects of histone deacetylase

inhibition in other organisms, such as yeast (see, for example, paragraph bridging pages 13 and 14). Therefore, Applicants submit that one skilled in the art, viewing the specification, would have recognized that the currently claimed methods, as exemplified in Drosophila, would reasonably be effective to increase activity of at least one gene encoding a protein selected from superoxide dismutase, cytochrome P450, or glutathione S transferase to extend the life span of other organisms.

In further support of this position, Applicants point out that there is no reason to believe that the exemplified method of extending the life span of an organism by contacting the cell with an inhibitor of histone deacetylase would not similarly be effective with respect to other types of organisms containing genes that encode a protein selected from superoxide dismutase, cytochrome P450 or glutathione S transferase. For example, Lea et. al. (Anticancer Res. 1999 May-Jun. 19(3A): 1971-6, a copy of which is attached as Exhibit A), describe use of 4-phenylbutyrate, the same compound exemplified in the current specification, and structural analogs, to effectively inhibit histone deacetylase in several different cell types, as well producing the similar downstream effect of inhibiting cell growth. For example, Lea et. al. reported that 4-phenylbutyrate inhibited histone deacetylase in both mouse erythroleukemia cells and human leukemic cells thereby inhibiting growth of these cells.

Lea et al. further reported that other compounds, including structural analogs of 4-phenylbutyrate, similarly inhibited histone deacetylase in such cells. Applicants point out that Lea et. al. is cited in the current specification at page 20, lines 20-23. The results reported by Lea et al. confirm that, as disclosed in the subject application, agents that inhibit histone deacetylase effectively decrease histone acetylation in multiple cell types and produce downstream effects similar to those reported for 4-phenylbutyrate in the cells of various organisms. Accordingly, Applicants submit that undue experimentation would not required for one skilled in the art to practice the invention, using the guidelines and procedures presented in the specification to extend the life span of various types of cells and other organisms. For example, those of skill in the art would know how to contact an organism with an inhibitor of histone deacetylase to increase activity of genes associated with free radical resistance selected from superoxide dismutase, cytochrome P450, and glutathione S transferase.

As is well known in the art, free radical activity in living organisms is a leading cause of aging, and disease. Hence, utilizing the invention methods that promote free radical resistance, those of skill in the art would readily succeed in extending the life span of the organism treated according to the invention methods.

In summary, the specification discloses that an inhibitor of histone deacetylase can promote free radical resistance of a cell so as to extend the life span of the organism, and exemplifies the claimed methods using the compound 4- phenylbutyrate in Drosophila cells. The Specification also teaches that Drosophila cells are a model system predictive of outcomes in other organisms.

Accordingly, it is submitted that one skilled in the art, viewing the subject application, would have known how to practice the claimed methods without undue experimentation, and further that histone deacetylate inhibiting compounds other than 4-phenylbutyric acid would be effective for increasing activity of genes associated with free radical resistance to extend the life of treated organisms. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

D. Prior Art Rejections

Applicants respectfully traverse the rejection of claim 1 under 35 U.S.C. § 102(a) as being anticipated by Imai et al., Nature 403, 795-800 (2000). Claim 1 has been cancelled, thereby rendering the rejection moot. However, in order to be fully responsive to the Office Action, Applicants will address the rejection as to new claims 33-43.

Rejection of a claim under 35 U.S.C. § 102(a) requires that the reference describe all of the elements and all of the limitations of the rejected claim. The current claims are directed to a method of extending the life span of an organism by administration of an effective amount of an inhibitor of histone deacetylase. Applicants teach that an effective amount of a histone deacetylase inhibitor is an amount sufficient to increase activity of genes associated with free radical resistance. Such genes are disclosed as including genes that lead to expression of superoxide dismutase, cytochrome P450, and

glutathione S transferase. By contrast, Imai et al. describe the administration of trichostatin to extend the life span of yeast. The teachings of Imai et al. do not describe extending life span of an organism by administration of a histone deacetylase inhibitor in an amount effective to increase activity of genes encoding superoxide dismutase, cytochrome P450, or glutathione S transferase.

Therefore, as Imai et al. fail to disclose each and every element of claims 33-43 as now presented, Applicants submit that anticipation has not been established over Imai et al. As such, Applicants respectfully request reconsideration and withdrawal of the rejection.

Applicants further traverse the rejection of claims 1-5 under 35 U.S.C. § 102(b) as being anticipated by Nudelman et al., Journal of Medicinal Chemistry (abstract). Claims 1-5 have been cancelled, thereby rendering the rejection moot. However, in order to be fully responsive to the Office Action, Applicants will address the rejection as to new claims 33-43.

The rejection of a claim under 35 U.S.C. § 102(b) requires that the reference describe all of the elements and limitations of the rejected claim. Nudelman et al. describe the administration of the histone deacetylase inhibitor glycerol tributyrate as an antitumor agent, thereby extending the life span of a treated animal having a B16F0 melanoma primary cancer. However, Nudelman et al. do not teach a method of extending life span of an organism by administration of an inhibitor of histone deacetylase to increase activity of genes encoding superoxide dismutase, cytochrome P450, or glutathione S transferase, as currently claimed in the present invention.

Therefore, because Nudelman et al. fail to disclose all the elements of the currently claimed methods, Applicants respectfully submit that anticipation has not been shown over Nudelman et al. Reconsideration and withdrawal of the rejection, therefore, are respectfully requested.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Respectfully submitted,

Date: April 15, 2004

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1: Anticancer Res. 1999 May-Jun;19(3A):1971-6. Related Articles, Link

Induction of histone acetylation and growth regulation in eryrthroleukemia cells by 4-phenylbutyrate and structural analogs.

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The objective of this investigation was to study the relationship between histone acetylation and growth inhibition by 4-phenylbutyrate and structural analogs. Inhibition of growth of DS19 mouse erythroleukemia cells and K56 human leukemic cells by 4-phenylbutyrate did not appear to be mediated by glutamine depletion. Vanadate blocked differentiation of DS19 cells but did not affect the hyperacetylation of histones. 2-phenylbutyrate was a more effective inhibitor of cell proliferation than 3-phenylbutyrate but was less effective as an inducer of histone acetylation. 4-Phenylbutyrate was a more effective inhibitor of histone deacetylase and inducer of histone acetylation than the structural analogs examined including 2- and 3-phenylbutyrate, cinnamate, methoxycinnamate, 2-phenoxybutyrate and phenoxyacetate.

PMID: 10470142 [PubMed - indexed for MEDLINE]